THE THERAPEUTIC USE OF TUBERCULIN: A WORKING HYPOTHESIS AND SOME PERSONAL OBSERVATIONS.[1]

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When I contemplated presenting to you my experience with tuberculin, my memory carried me back to the time some twelve years ago when I first began to use tuberculin under Dr. Trudeau's direction and inspiration. It is needless for me to say that I doubt if I would have begun its use at that time unless his faith had been so sure and strong that it was of some benefit. In 1900 Koch's original tuberculin had been in use nine years and his new tuberculin (T. R.) was some three years "old." Many modifications had already been tried: Hunter's, Trudeau's, etc.; Brehmer and Hahn had described their tuberculoplasmin and Klebs had learned at that time that antiphthisine did not fulfil his expectations. In 1900 I gave T. R. and a year later tuberculol of Landmann, a powerful poison which killed even normal guinea-pigs. The next year Koch described bacillary emulsion, and before long we were using that form of tuberculin. Since then I have used other forms of tuberculin, the broth filtrate, endotin, Beraneck's, old tuberculin, and mixtures of some of these forms.

To use any therapeutic means intelligently, to obtain its best results, and to advance the treatment of the disease by its exhibition, we should have in mind some reason for the faith that leads us to use it. I claim no originality for many of the following views which I have gathered from many sources, nor am I unaware that many objections, and some well founded, may be raised to these views, but they have afforded me a working hypothesis and as such I give them.

A Working Hypothesis. It is a well-known fact that normal animals do not react to tuberculin, and show, even after repeated doses, no sensitiveness to it as indicated by the ordinary tuberculin tests or reactions. The tuberculin reaction depends upon the presence of tuberculous tissue in the organism. The mere presence of dead or living tubercle bacilli in the body is not sufficient for a tuberculin reaction. The difference between normal and tuberculous animals lies in the fact that the latter possess tuberculous tissue, where is formed spontaneous tuberculin which in some way renders the animal sensitive to tuberculin. It is probable that normal animals possess no so-called receptors for tuberculin which is therefore inert when injected into their bodies.

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These receptors, or antibodies, are probably first formed in the focal (epithelioid) cells of the tuberculous tissue, cells which owe their formation to the irritation of the tuberculous poison and would seem therefore to possess from the beginning receptors for the poisons that have called them into existence. These cells are phagocytic and ingest tubercle bacilli, some of which they break down. What part the serum plays in setting free the protein portion of the tubercle bacilli, which is the active constituent of tuberculin, cannot be determined. It is this tuberculous protein, this primary protein as we may call it, that in all probability, sensitizes the body cells and is found in greatest concentration in the tubercle.

At this stage we might consider that the tubercle is composed of focal (epithelioid) cells, which contain tubercle bacilli in all stages of disintegration, primary protein and primary protein which has been acted upon by complement, either through the agency of some intermediary substance or possibly alone. This secondary substance, which if we like we may call anaphylatoxin, is what is concerned with the general and febrile reaction. The central nervous system and the tuberculous foci are most sensitive to this poison which often produces marked depression without general reaction or the usual fever. This explains what happens in many chronic cases, when without much fever and without apparent reaction they gradually lose weight and falling into a state of malnutrition, die finally from asthenia. The primary tuberculous protein is capable of sensitizing or stimulating cells in other parts of the body through, I believe, some agency arising in the tubercle. We may call it receptor, antibody, or amboceptor to facilitate discussion. Arising first in tuberculous tissue in the focal cells, these antibodies are in greatest concentration in the focus but later in the course of the disease are formed in other parts of the body. It is probably through these antibodies or amboceptors, that the injected tuberculin and complement are drawn into or fixed in the focus, thus producing focal reaction. Complement may be present in such small amounts that some time must elapse before a sufficient amount is fixed to produce the local reaction. In certain methods of application (cutaneous and ophthalmic tests) the amount of tuberculin absorbed depends, *cœteris paribus*, upon the time the tuberculin is in contact with the skin or conjunctiva. If, as occurs in the subcutaneous injection of tuberculin, only a small fraction of it is fixed at the site of injection, the remainder is absorbed into the circulation.

These receptors are most numerous in the focus whither most of the injected tuberculin finally finds its way and is fixed by the receptors. The period of incubation, the time between the injection of tuberculin and the general reaction depends upon the time required to bring enough injected tuberculin and tuberculin in the focal cells together with the antibody and complement to set free sufficient anaphylatoxin to cause the general reaction. The union in the focus produces the focal reaction which brings about the hyperemia.

In tuberculin treatment the quantity of tuberculin injected usually falls short of the quantity necessary to enable the complement to set free sufficient anaphylatoxin to produce a general reaction but does cause a focal reaction. These focal reactions stimulate the formation of antibodies some of which are thrown off into the blood stream. In a few cases they occur spontaneously, but more often they are found only after larger doses of tuberculin. Termed usually antibodies, they may be said to include agglutinins, precipitins, bacteriolysins, opsonins, and complement deviating substances (antituberculin), etc. These substances, however, have not yet been causally connected with clinical improvement, or indeed, with sensitiveness to tuberculin. When large doses of tuberculin are reached without reaction, that is, tuberculin tolerance is acquired, it is possible that some of the free antibodies may partially neutralize the injected tuberculin, so that larger doses are required to produce reaction in even the most acutely sensitive cells of the tuberculous foci, while the cells in other parts of the organism, needing a greater stimulus to produce a response, fail entirely to react. This "neutralization" of tuberculin may rest only in part upon the presence of antibodies, and may depend more upon the increasing lytic activity of the complement. By this I mean that the splitting of the tuberculous protein may be so great that the stage of anaphylatoxin is entirely passed over, which probably occurs during pancreatic digestion of protein. It may again be explained by the failure of the complement to split up the primary protein (the injected tuberculin) which then calls forth a superabundance of antibodies or amboceptors, which would lead later, with an efficient complement, to the more intense disintegration of the tuberculin. It is also of interest to note that in some patients, when tuberculin is beneficial, it seems to bring about improvement in symptoms almost with the first dose.

Now focal reactions may lead on the one side to absorption of tuberculous tissue, due no doubt to the greater blood supply there present at that time, an idea which is based upon Bier's work on the effect of hyperemia upon chronic inflammation. On the other side, they may produce demarcation, softening, and destruction of the focus, which in turn may lead to deposition of lime salts or replacement by fibrous tissue.

The failure of tuberculous individuals to react to tuberculin may be due to the neutralization of the injected tuberculin by the presence of antibodies in the body juices, or again to the failure of the body to produce complement in sufficient amount to cause reaction, or rather to the production of complement which is not sufficiently lytic to split up the injected tuberculin.

Hypersensitiveness is difficult to explain. The facts are that after an overdose of tuberculin the patient may become extremely sensitive to greatly reduced doses. This would indicate either an increased formation of the split product of the tuberculin anaphylatoxin, or increased susceptibility of certain cells of the body to the poison. Now patients who are doing well clinically, as well as some with active or subacute symptoms, may both present this phenomenon, which appears therefore to be favorable as well as unfavorable. An increased formation alone of anaphylatoxin would account for its unfavorable action, but this alone can hardly be the only cause, for it must also be increased in the favorable cases. Here the immunity mechanism seems so adjusted that whatever spontaneous primary protein escapes from the focus is immediately disintegrated, that is, the lytic process, set up by the complement, is so active that anaphylatoxin is never formed, and the lysis carries the splitting process on to the formation of simpler bodies. Now when a sufficient amount, however small, of tuberculin (primarily protein) is injected into the body, it changes this favorable balance and the action is not carried on so far and anaphylatoxin results. If perchance through overexertion a focus is flooded or washed out by an increased blood flow, so much more primary protein than usual escapes that it cannot be split up beyond anaphylatoxin, general and focal reactions occur and recur, which today some call excessive auto-inoculation. To stem these is at times difficult, and their result is disastrous.

It has been held that tuberculin does not act like other proteins, such as serum or egg white, in the production of anaphylaxis. A minute quantity of horse serum, injected into an animal previously sensitized with it, produces anaphylactic symptoms. The second injection may be introduced in any way and anaphylaxis results. This is not true of tuberculin. When, for instance, a normal guinea-pig is sensitized with a small quantity of tuberculin, enough, for example, to produce a skin reaction in a tuberculous guinea-pig, which is 0.02 c.c., and a second small dose is injected into the skin, muscles, or peritoneum, nothing results. If, however, a larger dose is injected, or if a very small dose is injected into the cerebral cavity or intravenously, anaphylactic symptoms supervene.

Recent work has shown that serum is the most concentrated form of protein solution that we have. Attempts to concentrate the primary protein of the tubercle bacillus lead to the conclusion that the greater dilution of this protein may explain many of the differences in action between it and serum. There is, however, a further difference that must be noted. To bring about tuberculin anaphylaxis, strong concentrations of tuberculin must be brought in direct contact with the cells of the central nervous system.

THERAPEUTIC ADMINISTRATION. Turning now to the practical therapeutic administration of tuberculin, I might repeat what I said six years ago, namely, that the most important point in the tuberculin treatment is the dosage. At that time I predicted that the opsonic index would never be generally adopted as a guide to the individual dose. Since that time the cutaneous and ophthalmic tests have been widely employed, and some have made use of them in determining the individual dose, as I shall mention a little later.

Many sites of administration of tuberculin have been employed, such as the oral, rectal, vaginal, intratracheal, intravenous, cutaneous, intracutaneous, subcutaneous, and the inhalation methods. For one reason or another, the majority of these have been discarded, and tuberculin is now usually injected under or into the skin. The intravenous method has some possibilities, but Koch and his followers who made use of it were never very enthusiastic about it and few have employed it.

PREPARATIONS FOR ADMINISTRATION. How long tuberculin retains its strength in solution has never been determined. Strong solutions (7.5 per cent.) appear to retain some of their reacting powers at the end of two to three years. Weaker solutions may deteriorate much more quickly, and I have used dilutions, freshly prepared, every two weeks. As a diluent, ¼ per cent. phenol in physiological saline has been used, but the phenol can be replaced by lysol. A 10 c.c. cylindrical graduate, an ordinary tuberculin syringe, and a bottle of sterile physiological salt solution, preferably with a syphon or a stop-cock inserted at the side, enable one to make the dilutions in a very few minutes. Each dilution is $\frac{1}{10}$ the strength of the preceding.

The skin should be rubbed with alcohol and the needles sharpened each day before use. A very fine needle should be used.

VARIETIES OF TUBERCULIN. The forms of tuberculin which I have used might be grouped under three heads:

1. Those forms of tuberculin which consist of extracts of tubercle bacilli or substances secreted during their growth, if such exist. Koch's original tuberculin is the best example of this class. Among other forms I have used Landmann's tuberculol, Denys's broth filtrate, Beraneck's tuberculin, tuberculin A. F., Gabrilowitch's endotin.

2. Tuberculin composed of the body substance of the tubercle bacillus, of which I have used T. R. and B. E.

3. I believe I was the first to suggest the use of these two types of tuberculin together. A compound known as B. F. Co. consists really of a mixture of broth filtrate and bacillary emulsion in the proportion of 5 to 2 by volume. This form of tuberculin contains every product of the tubercle bacillus, unaltered by heat and theoretically appeals to me very much.

Practically, I might say that I have not noticed any difference in the action of the various types of tuberculin save that some are more poisonous than others.

DOSAGE. When I first began to give tuberculin in 1900 I used the doses advocated by the makers of the various tuberculins which I employed. Accordingly, for O. T., the first dose was 0.1 mg. ($\frac{3}{1}$), for T. R., 0.002 mg. ($\frac{5}{2}$),[2] and for B. E. 0.0025 mg. ($\frac{5}{25}$) solid substance. Later it seemed to me that when much smaller beginning doses ($\frac{8}{1}$ or even $\frac{9}{1}$) were employed, the patients reacted to much smaller quantities of tuberculin. Anaphylaxis had not been described at that time, but certainly many patients seemed to exhibit marked susceptibility to very minute doses. More recently I have again employed larger beginning doses, and frequently give 0.000001 or even 0.00001. These doses cause no reaction in many patients, but a few become hypersensitive, and I am never able to increase the dose very much.

METHODS OF ADMINISTRATION. There are two methods of giving tuberculin which have different aims in view. The usual method, that described by Koch and modified by Trudeau and others, is to give a dose much below that required to produce a reaction, and by gradually increasing the quantity, to bring about immunity or better, tolerance, not to the tubercle bacillus, but to tuberculin itself. I have employed this method for years, but always realized that it fell far short of what was required for the most successful treatment. When the discovery of opsonins was announced I hoped that the opsonic index would give us the criterion that we needed to select at each injection the optimum dose. It is needless for me to say that the method presents too many difficulties, too many uncertainties, to enable it to be employed for such purposes. In many patients it is not difficult to bring about a marked tolerance to most tuberculin, and there is some evidence to show that patients who take tuberculin well have a tolerance to it which may have been established before tuberculin treatment had been begun. One patient recently received as an initial dose, 0.00001 ($\frac{4}{1}$) B. F., and in one hundred and fourteen days was given 33 doses, the last being 1000 mg. of B. F., without suffering a reaction or inconvenience at any time. The patient did very well, but was it on account of tuberculin? I question it. Others started about the same time have never been able to take a dose as large as this. They have not done so well.

Where tuberculin tolerance is wished, it seems to me safe to give, say $\frac{8}{1}$ O. T. in 0.1 c.c. of diluent, intradermically, and to increase the dose tenfold twice a week ($\frac{7}{1}$, $\frac{6}{1}$, $\frac{5}{1}$, $\frac{4}{1}$) until the local skin reaction begins to be marked. In one case with extensive physical signs, good general condition, and few symptoms, I reached a subcutaneous dose of $\frac{3}{1}$ O. T. in six to seven weeks with only fairly marked intradermic reactions. Such a patient has a large number of highly sensitized areas in his skin which may possibly throw off antibodies into the blood. The beginning dose may in most cases be much higher without fear of reaction. Such a method would quickly lead to doses that cause response in the organism, and so bring about the formation of antibodies which occur more often with large than with small doses.

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[2] "$\frac{5}{2}$" represents a convenient abbreviation for 0.000002 g. or c.c.

The rate of increase of the dose early interested me as I found that when I increased the dose by tenths of a cubic centimeter of the various dilutions (each of which is always ten times the strength of the preceding) I frequently obtained reactions when I increased from 1 to 2 or from 2 to 3 tenths. This led me to interpolate 1½ and 2½ tenths and to drop out 7 and 9. Later, with the aid of the late Mr. Pope, I constructed a logarithmic scale in which the increase was by geometrical proportion. This was based upon Fechner and Weber's law, namely, to increase the reaction in arithmetical proportion it is necessary to increase the stimulus in geometrical proportion. This table enables me to increase the dose from 0.01 to 1 c.c. of any dilution, using any rate of increase that I wish to select from 300 per cent. down to 12 per cent. I usually employ a rate of increase of 50 per cent. and find reactions no more likely to occur at one point of the scale than another.

The intervals are usually three or four days for the smaller doses and seven days for the larger doses.

The second method of giving tuberculin depends upon repeating the same dose at much longer intervals. Wright was the first to suggest such a method of treatment. I confess that I have never used the opsonic index method for it appeared to me from the start as impracticable. Good results have been reported by this method but Wright early stated that auto-inoculation was so frequent and so easily produced in pulmonary tuberculosis that his method was of little avail. On the other hand, Kinghorn and Twichell showed when an attempt was made to attain tuberculin tolerance, irrespective of the opsonic index, and the dose given in either the negative or the positive phase, the results were about the same. The opsonic index they concluded could be disregarded when tuberculin tolerance was aimed at. Many of us who have given tuberculin have, from time to time, received accidental inoculations which resulted in severe reactions. After recovering from such a reaction many experience a pronounced feeling of well being, which is so marked in some patients after the tuberculin test, that they have requested me to give them the tuberculin treatment. Such facts led W. C. White to attempt to estimate for each patient the dose of tuberculin that will just fall short of a fairly marked reaction. He makes use of the cutaneous test and applies a definite quantity of tuberculin to an abrasion made so deep that the pink of the corium can be seen without producing any exudation of serum or blood. He then covers the tuberculin with a vaccination shield and allows it to dry *in situ*. When the cutaneous reaction at the end of the forty-eight hours has not exceeded 5 mm. he calls it the desired reaction and proceeds to give this dose, not subcutaneously, but in the lower layers of the skin where it causes a local or "Stichreaktion" of 20 to 40 mm. in diameter. If given oftener than every two weeks, he believes the patient acquires tolerance for tuberculin and so his interval is two weeks. I cannot subscribe to all the details of this method but in certain cases it is of apparent usefulness.

I shall not attempt to go into any details about increasing the dose when tuberculin tolerance is the aim. A good general rule is never to increase the dose when there has been any pronounced deviation from the usual trend of the disease. Another rule is when in doubt about giving an increased dose, do not do so. A very curious thing is that when tuberculin helps a patient very much, small doses appear to have as beneficial effects, certainly upon the symptoms, as larger. Tuberculin treatment, whatever working hypothesis is adopted, must be looked upon as a method of active immunization. Since this is the fact, it is useless to expect body cells, already flagging, to react with an adequate response. At such periods, tuberculin treatment should be omitted.

THE RESULTS. The goal of treatment in every patient is the cure of his disease or the alleviation of his symptoms. The estimation of the results of such treatment, however, is not always easy, for in many instances at least two personal equations enter, that of the patient and that of the physician. I am convinced that the explanation of the excellent results reported, for example, in pulmonary tuberculosis by the use of such substances as urea, sanosin, lignosulphite, griserin, nucleic acid, hetol, etc., are due far less to the action of the drug *per se* than to the effect of suggestion on the patient, perhaps unconsciously exerted, through the faith of the physicians who have first employed them. Certainly most of them when given as it were "in cold blood" produce such poor results that their use has been largely discontinued. Tuberculin cannot escape this weakness and indeed I believe its value can be greatly enhanced when the administrator has implicit faith in its curative properties and imparts that faith to his patients. The scientific physician of today who keeps faith with himself and refuses in such chronic and relapsing diseases as pulmonary tuberculosis to promise a "cure" to any patient by the use of any means, will certainly divest that means of a certain amount of suggestion and may rob it of some results that an absolute believer could impart to it. Such a believer, however, can get no idea how much of the results are due, for example, to tuberculin and how much to the faith he has imparted to his patients. However, I am not here to discuss suggestion or auto-suggestion but the effect of tuberculin. I might say that the only suggestion I employ in connection with tuberculin is auto-suggestion by the patient. I try to be frank with him and tell him at the outset that tuberculin may help him and will not harm him if properly given, for of this I feel sure. One of my friends, whose faith in tuberculin is such that he can I believe honestly promise his patients that he will cure them with it, should get far better results than I, though he has never as yet collected his results.

Another factor which must be taken into account in discussing results of tuberculin treatment is the closer relationship that such treatment establishes between patient and physician. I must confess that I find it difficult to bring a patient to my office twice a week for months and discuss symptoms and fears, one of which gradually grows less while the other is often replaced by more or less indifference, borne of familiarity. When, however, I give this patient tuberculin, he and I can discuss his case in detail twice a week and I am able to discover slight but important changes in his condition, to check imprudence, and to change needless timidity into confidence in his ability to order aright his life. I cannot but believe that such a patient has a very great advantage over another who takes no such treatment. These factors must be taken into account in any treatment and I am convinced affect materially the results.

THE EFFECT UPON SYMPTOMS. The symptomatic effect of tuberculin demands careful study and observation during treatment. Much work has been done upon the blood. It was early stated that tubercle bacilli were mobilized and occurred in the blood during the tuberculin reaction, but trustworthy evidence has never been produced that such is the case. The leukocytes show an essential increase, rarely over 10,000 per cubic millimeter and Arneth's neutrophilic picture may be shifted to the right and so approach nearer normal. In some instances, especially after large doses, agglutinins, precipitins, opsonins, and complement deviating substances occur in the serum. The urine may show a diazo reaction at the height of a general tuberculin reaction but does not do so otherwise. Some believe the quantity of urine is increased. The weight may decrease slightly after large doses and especially after reactions but when the course is finished the weight often increases rapidly. The appetite is usually unaffected except with reaction, but may be improved. The strength is quickly affected when the doses are too large. A feeling of discomfort, of ill-being, even malaise, may occur without rise of temperature. They indicate tuberculin poisoning and must be avoided. When the temperature varies from 99° to 100° F., following each dose it may be lowered or fall to normal. In other patients a slight temperature of 99.5° F. becomes normal and remains so but in a few rises again when treatment is stopped. Rise of temperature may not occur until the patient is severely poisoned with tuberculin and must not be considered the sole guide to dosage.

The localizing symptoms may be increased or diminished according to the effect of the dose. The cough and expectoration may be lessened with each dose in such a way that the patient calls attention to it. Such a dose should always be repeated as long as such favorable results are obtained. In others the cough and expectoration increase with each dose and the treatment has to be abandoned. Usually there is no effect noticeable one way or the other. The virulence and morphology of the tubercle bacillus are apparently unaffected, but more patients taking tuberculin seem to lose their bacilli. This is especially true for the moderately advanced patients. Oppression in the chest is not uncommon, while pleurisy can rarely be attributed to tuberculin.

The physical signs may be increased, but it is more often difficult to detect during treatment any change in the physical signs other than what usually occurs from day to day in most patients.

My experience leads me to believe complications occur less frequently among patients receiving tuberculin treatment, but it does not exclude their occurrence.

THE UNTOWARD RESULTS. Tuberculin, like arsenic or strychnine is a powerful poison which, when used injudiciously, is capable of great harm. The disrepute into which tuberculin fell at first was due to the selection of patients who should never have received it and to faulty dosage and too short intervals. Coincidence undoubtedly accounts in part for some of the so-called "unfortunate results." The mobilization of tubercle bacilli in the body, claimed by some to occur after tuberculin, has never been proved to occur either clinically or experimentally. In over 10,000 injections, 11 instances of hemoptysis more or less closely connected with or at least following tuberculin (in one to three days) have come under the writer's notice. In none was it severe, in most slight, and in 8 a previous hemoptysis had occurred. I have given, together with my assistants, to some 200 to 300 patients from 10,000 to 20,000 injections and have observed but two unhappy results at the site of inoculation. In one, a patient received too large a dose of bacillary emulsion at a single point and developed a sterile abscess which was healed by aspiration without opening. The second patient had what seemed to me to be a neuritis, as there was little to be seen at the site of inoculation. It was exceedingly painful and prostrating and deterred me for many years from injecting tuberculin into the arm. I might add that I now nearly always give it in the arm.

I have seen patients taking tuberculin do badly and have seen complications arise which might be attributed to it. I have also seen the same complications occur in patients to whom we had thought of giving tuberculin. While I have tried to keep an open mind in regard to tuberculin, I may be somewhat prejudiced in its favor, though many of my colleagues in Saranac Lake would more readily believe the opposite. Consequently, when I say I have never seen any permanent untoward results to be attributed directly to tuberculin, I hope you will believe that I have tried to be fair.

There is some evidence, both experimental and clinical to show that tuberculin may cause nephritis, or at least, that it develops during treatment.

EXPERIMENTAL RESULTS. The results of treatment of tuberculous animals with tuberculin has not been satisfactory. Life has been prolonged and changes have occurred in the lesions which demonstrate an attempt at healing but cure or bacterial immunity has not been effected. Some deny the value of animal experimentation in regard to tuberculin in man and much slipshod work has been published. Today the value of tuberculin treatment for man rests largely upon the results obtained in man.

ULTIMATE RESULTS. The results in man have been for the most part good but many observers have failed to support their contentions with proof other than their personal belief or impressions.

Selection of patients certainly affects the results, and when only favorable cases with tubercle bacilli in the sputum are chosen, the results will be far better than when all patients are given the treatment. At the Adirondack Cottage Sanitarium we gave tuberculin to carefully selected patients for a time and then selected for a year or two the worst cases. Later we exercised no selection but allowed the patients to elect to take tuberculin treatment. We thought this would be the fairest test but in reality it has resulted in a selection against tuberculin as those patients who wished to stay a little longer because they were more advanced or ran a subacute course chose to take tuberculin. The patients we selected because they were the worst, did remarkably well. The results on the whole, when reduced to cold figures, with every error we could think of eliminated, showed that among the moderately advanced patients those who took tuberculin did better than those who did not, while for the incipient stage the difference was less pronounced. This held true for both immediate and ultimate results.

In the individual case, however, tuberculin often falls far short of what is hoped from its use. In early cases it is almost impossible to say how much good tuberculin does. In the more advanced cases favorable results are more often seen and in the very chronic cases the effect of tuberculin is in a few truly astonishing, so good, in fact, that no one questions it. It is these results that win for tuberculin its advocates and I am sure that after two or three such cases few would doubt its efficacy in some patients. When, however, results are tabulated and impartial statistical methods applied, they are so far from upholding the impressions created by these few cases that the statistical methods themselves, and not the results of tuberculin, are questioned.

My observation leads me to believe that incipient cases treated with tuberculin do somewhat better than those not so treated, while the moderately advanced cases do much better. The ultimate results do not show such marked differences, but indicate that the treated, both incipient and moderately advanced, do better.

REST VERSUS CLIMATE IN THE TREATMENT OF PULMONARY TUBERCULOSIS.[1]

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The world is still knocking at the door of the medical profession asking for a cure for its greatest scourge, and we who are particularly interested in the treatment of pulmonary tuberculosis are certainly anxious to unite upon some sane rational therapy pending the discovery of a true specific.

Phthisiotherapists agree upon but one point, namely, that tuberculosis is curable. Their mode of procedure in effecting this cure varies to a considerable degree. As an example of this, two years ago I was able to collect 75 varieties of tuberculin in the market, each with its champions and devotees, claiming some particular merit for their special brand, seemingly forgetful of the fact that tuberculin is a product of the tubercle bacillus, call it by what name you will, and that success in treatment depends not so much upon the form used as upon its dosage and mode of administration.

So has it been with other measures for the treatment of tuberculosis as its therapy has evolved through the centuries from Hippocrates and Aretaeus, who knew little about it, down to Robert Koch, who has given us our present-day conception of the disease. Climatic treatment ruled supreme for many years, and particularly in the United States. It became the rule when a patient was pronounced tuberculous to send him to another climate—warmer, drier, higher, or lower—than his own. Colorado, California, Arizona, and New Mexico became the favored resorts, the four

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